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Glomerular hemodynamics and hormonal evaluation during starvation in rats

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Glomerular hemodynamics and hormonal evaluation during starvation in rats. The effects of total food deprivation on renal function were evaluated in normal Munich-Wistar rats submitted to starvation (S) periods of two to eight days (Groups S_2 to S_8). A prompt and sustained decrease in renal plasma flow (RPF) and an increase in total renal vascular resistance (TRVR) were observed after the second day, together with a gradual decrease in glomerular filtration rate (GFR) until the fourth day (40% in the S_4 group, $P < 0.05$). After this period, a spontaneous and progressive increase in GFR occurred in spite of continuing low RPF and high TRVR. Glomerular hemodynamics were evaluated in additional animals from groups S_4 and S_7. As observed for whole kidney GFR, mean single nephron (SN) GFR was reduced in group S_4, but not in group S_7. The decline in SNGFR in S_4 was the result of a decline (~40%) in glomerular plasma flow rate (Q_A) and glomerular capillary hydraulic pressure (P_{GC}), due to a predominant increase (~60%) in afferent arteriolar resistance. In S_7, SNGFR and its determinants did not differ from the control. Angiotensin II (Ang II), prostanglandin (but not thromboxane A_2, TxA_2) inhibition blunted the alterations in whole kidney function observed in S_4. Conversely in S_7, the inhibition of vasoconstrictor agents (Ang II and TxA_2) did not normalize GFR, suggesting that the intrarenal vasoconstriction could be an important factor to maintain GFR after a prolonged period of starvation. Thus, prolonged starvation induces a biphasic profile of renal function in rats: a first phase characterized by a decline in GFR and SNGFR followed by an adaptative phase with normalization of GFR and superficial glomerular function. Results suggest that these physiological alterations are dependent on a complex hormonal relationship involving hormones such as Ang II and prostaglandins.

Important metabolic, hormonal and functional alterations are induced by starvation [1, 2]. This abrupt form of food restriction can induce adaptive mechanisms which permit survival for prolonged periods of starvation. Indeed, human beings can endure several months of fasting [3]. The renal functional responses to starvation are a reduction in glomerular filtration rate [4], natriuresis and polyuria [5]. However, the physiological mechanisms present in the kidney during progressive and prolonged periods of starvation are not fully understood, nor is it known whether renal function can adapt to total food deprivation. Thus, the objectives of the present investigation were to study the effects of progressive periods of starvation (S) during two to eight days (Groups S_2 to S_8) on renal function in rats, and to evaluate the glomerular hemodynamics and renal microcirculation during medium (S_4) and prolonged (S_7) periods of starvation. The role of hormones such as angiotensin II, prostaglandins and thromboxane A_2 in the alterations of whole kidney function induced by four and seven days of starvation was also evaluated. The results of the present study showed a biphasic profile of whole GFR and SNGFR with reduction during the first phase (4 days) followed by a spontaneous normalization in the late phase. The physiological alterations in the whole kidney function were dependent, at least in part, on angiotensin II and prostaglandins.

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Methods

Three sets of experiments were performed.

(1.) Whole kidney function. Male Munich-Wistar (MW) rats weighing 260 to 310 g were submitted to starvation periods of two to eight days (Groups S_2 to S_8), only with free access to water. After the starvation period, experimental and control animals were submitted to surgery under hydropenic conditions for whole kidney function evaluation as follows.

The animals were anesthetized with inactin, 100 mg/kg body wt i.p. (Byk Gulden, Konstanz, Germany) and placed on a temperature regulated table. Following tracheotomy, a polyethylene catheter (PE50) was introduced into the left femoral artery and connected to a direct-writing recorder (Gould model 2.200, Cleveland, Ohio, USA) for mean arterial pressure (MAP) measurements and collection of blood samples. The left jugular vein was catheterized (PE50) for infusion of 10% inulin and 2% p-amminohippuric acid (PAH) at a rate of 1.2 ml/hr. After laparotomy, a catheter (PE10) was inserted into the left ureter for urine sampling and urinary flow rate determination.

After a 45-minute equilibration period, glomerular filtration rate (GFR) and renal plasma flow (RPF) were evaluated by inulin [6] and PAH [7] clearances, respectively. Total renal vascular resistance (TRVR) was estimated as the MAP-3/[RPF/(1-Hct)] ratio, and the filtration fraction (FF) by the GFR/RPF ratio. GFR and RPF are expressed per gram of kidney weight.

Plasma protein levels were determined with a refractomer and corrected on the basis of a standard curve constructed by the method of Lowry, modified by Schachterle [8]. Plasma protein was also determined by the fluorcolorimetric method of Viets et al [9].

(2.) Glomerular hemodynamic evaluation. Starvation induced important alterations in kidney function (**Results**), which were more prominent in groups S_4 and S_7. Thus, glomerular hemodynamics were evaluated by the micropuncture technique

Table 1. Effect of starvation lasting two (S_2) to eight (S_8) days

Group	Body wt		Kidney wt	MAP	Hct_o	Hct	C_{Ao}	C_A
	Before	After	*g*	*mm Hg*	%		*g/dl*	
Control (N = 14)	292 ± 6	—	0.83 ± 0.02	100 ± 3	44 ± 1	47 ± 1[c]	5.9 ± 0.2	5.3 ± 0.3
S_2 (N = 5)	293 ± 1	264 ± 1[a]	0.79 ± 0.02	99 ± 3	50 ± 1[b]	55 ± 1[c]	5.5 ± 0.1	5.4 ± 0.3
S_3 (N = 7)	309 ± 7	271 ± 7[a]	0.86 ± 0.03	105 ± 6	51 ± 1[b]	54 ± 1[c]	5.7 ± 0.1	5.0 ± 0.1
S_4 (N = 6)	292 ± 4	228 ± 4[a]	0.73 ± 0.02[b]	96 ± 5	52 ± 1[b]	56 ± 1[c]	5.7 ± 0.1	4.8 ± 0.2[b,c]
S_5 (N = 10)	294 ± 6	239 ± 7[a]	0.72 ± 0.02[b]	100 ± 4	50 ± 1[b]	54 ± 1[c]	5.2 ± 0.1	4.6 ± 0.1[b,c]
S_6 (N = 8)	289 ± 9	222 ± 7[a]	0.72 ± 0.02[b]	97 ± 2	50 ± 1[b]	53 ± 1[c]	5.2 ± 0.1	4.6 ± 0.1[b,c]
S_7 (N = 5)	319 ± 10	237 ± 9[a]	0.72 ± 0.04[b]	92 ± 4	52 ± 2[b]	54 ± 2	4.9 ± 0.2[b]	4.5 ± 0.2[b,c]
S_8 (N = 5)	307 ± 4	225 ± 8[a]	0.74 ± 0.04[b]	95 ± 8	53 ± 1[b]	54 ± 1	4.8 ± 0.2[b]	4.3 ± 0.1[b,c]

Abbreviations are: body wt, body weight; kidney wt, kidney weight; MAP, mean arterial pressure; Hct, hematocrit; and C_A, plasma proteins. The "$_o$" index corresponds to the initial values, obtained about 20 minutes after anesthesia.

Data are X ± SE.

[a] $P < 0.05$ vs. before starvation; [b] vs. control; [c] vs. initial values

in additional Munich-Wistar rats from the control (C, N = 7), S_4 (N = 8) or S_7 (N = 6) groups. The animals were submitted to the same surgical procedures as described above. After ureter catheterization, the left kidney was prepared for the micropuncture study, as previously described and established in this Laboratory [10, 11]. Briefly, fluid samples were obtained from surface proximal tubules of at least three nephrons over a period of one to three minutes. At the time of fluid collection, blood was also obtained from the femoral artery for plasma inulin determination by the anthrone method [6]. Inulin concentration in tubular fluid was determined by the microfluorescence method [12].

Blood samples from three or four superficial efferent arterioles were collected and analyzed for protein concentration (C_E). Pre-glomerular protein (C_A) was estimated from femoral arterial plasma. C_A and C_E were determined by the fluorimetric method of Viets et al [9].

Finally, hydraulic pressures were measured in superficial renal microstructures using a continuous recording servonull micropipette transducer system (IPM Inc, San Diego, California, USA). Micropipettes with outer tip diameters of 2 to 4 μm filled with 2.0 M sodium chloride were introduced into superficial structures. Hydraulic pressure output from the servosystem was channeled by an electronic transducer (Statham model P23Db) to a second channel of the recorder. Direct measurements were obtained from glomerular capillaries (P_{GC}), proximal tubules (P_T), efferent arterioles (P_{EA}) and peritubular capillaries (P_C).

The following glomerular function data were obtained: single nephron glomerular filtration rate (SNGFR) and filtration fraction (SNFF), glomerular capillary plasma flow rate (Q_A), afferent (R_A), efferent (R_E) and total ($R_T = R_A + R_E$) arteriolar resistance, and glomerular ultrafiltration coefficient (K_f). The equations of Deen, Robertson and Brenner [13] were used for the calculations.

(3.) Hormonal participation. The effects of angiotensin II (Ang II), prostaglandin (PGs) and thromboxane A_2 (TxA_2) inhibition on whole kidney function were evaluated during two distinct periods of starvation (4 and 7 days). Male MW rats were chronically treated (4 or 7 days) with captopril (Cp), an angiotensin I converting enzyme inhibitor, or indomethacin (Indo), a cyclooxigenase blocker, or dazmegrel (Daz), a specific thromboxane synthesis inhibitor. Thus the following groups were formed: S_4 + Cp (N = 8) and S_7 + Cp (N = 7) received Cp (SQ 14.225, Squibb and Sons, USA), 50 mg% in drinking water, during four or seven days of starvation; S_4 + Indo (N = 7) and S_7 + Indo (N = 7) received Indo (Merck Sharp & Dohme Ind. Quimica and Famacêutica Ltd, Brazil), 2 mg/kg/day, i.p.; S_4 + Daz (N = 6) and S_7 + Daz (N = 6), received Daz (UK-38485, Pfizer Central Research, England, UK), 50 mg/kg/day per os.

Statistical analysis

Statistical analysis was performed by Kruskal-Wallis Analysis of Variance followed by the Dunn test. Statistical significance was defined as at least $P < 0.05$. All data are reported as mean ± SE.

Results

The results obtained for the control and S_2 to S_8 groups are summarized in Table 1.

Mean body weight loss was already significant on the first day of starvation. Kidney weight was also reduced, but the reduction was significant ($P < 0.05$) only after the fourth day. Mean arterial pressure (MAP) was unchanged by starvation.

Initial hematocrit (Hct_o) was elevated in all starved groups when compared with control ($P < 0.01$). Since the animals were hydropenic, an expected additional elevation in Hct was observed in all groups during the experimental period. Initial total plasma proteins (C_{Ao}) were significantly reduced only in groups S_7 and S_8 ($P < 0.001$).

Figure 1 and Table 2 show the daily effects of food restriction on glomerular filtration rate (GFR), renal plasma flow (RPF) and total renal vascular resistance (TRVR). During the eight day period of the study, GFR exhibited a bimodal profile with a progressive decline up to the fourth day (S_4), when the reduction was 40% of the control values, 0.92 ± 0.06 versus 0.57 ± 0.05 ml/min ($P < 0.001$). Thereafter, GFR rose progressively and spontaneously despite continuous starvation. The GFR of groups S_7 and S_8 was similar to control values, that is, 0.84 ± 0.07 ml/min and 0.8 ± 0.02 ml/min, respectively. RPF decreased and TRVR increased abruptly and significantly on the second day, and both were different from control values throughout the period of food restriction.

Table 3 summarizes the mean values for the micropuncture data obtained for groups C, S_4 and S_7. As observed for total GFR and RPF, single nephron GFR (SNGFR) and glomerular

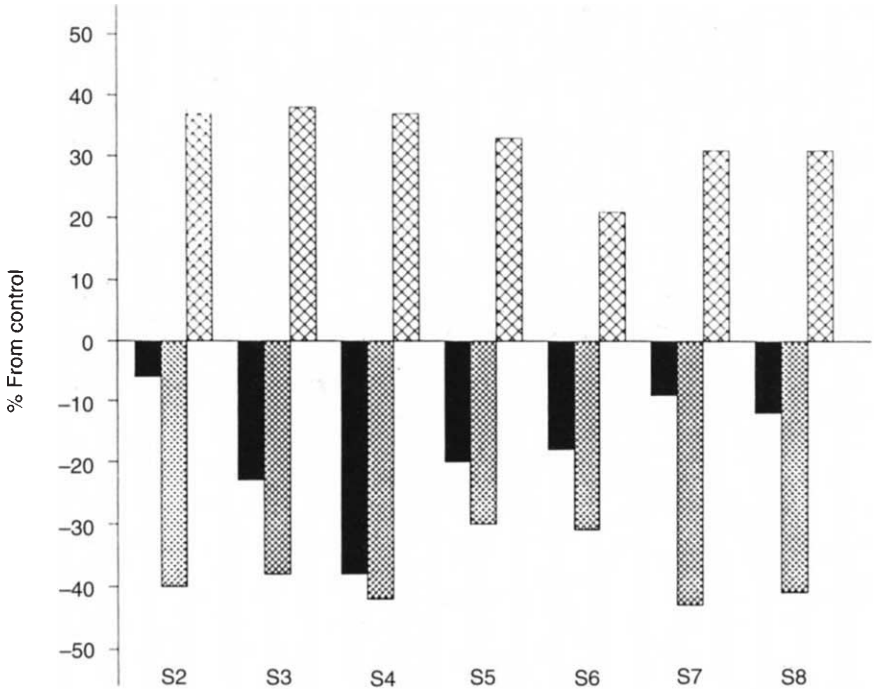

Fig. 1. *Percent change in glomerular filtration rate (■), renal plasma flow (▦) and total renal vascular resistance (▩) in relation to the control group (baseline).*

Table 2. Whole kidney function for all groups

Group	V′	GFR	RPF	FF	TRVR
	μl/min	*ml/min*		%	*mm Hg · min · ml*$^{-1}$
Control (N = 14)	2.1 ± 0.2	0.92 ± 0.06	3.69 ± 0.26	26 ± 1	14.7 ± 1.2
S_2 (N = 5)	1.5 ± 0.1[a]	0.87 ± 0.03	2.22 ± 0.18[a]	40 ± 3[a]	20.1 ± 1.3[a]
S_3 (N = 7)	1.3 ± 0.2[a]	0.71 ± 0.07[a]	2.52 ± 0.22[a]	29 ± 3	20.2 ± 2.4[a]
S_4 (N = 6)	1.8 ± 0.2	0.57 ± 0.05[a]	2.15 ± 0.26[a]	28 ± 2	20.1 ± 2.9[a]
S_5 (N = 10)	1.4 ± 0.1[a]	0.74 ± 0.08[a]	2.58 ± 0.27[a]	29 ± 1	19.6 ± 2.4
S_6 (N = 8)	1.6 ± 0.2[a]	0.76 ± 0.07[a]	2.56 ± 0.17[a]	30 ± 3	17.8 ± 1.3
S_7 (N = 5)	2.5 ± 0.5	0.84 ± 0.07[b]	2.13 ± 0.11[a]	41 ± 4[a]	19.3 ± 0.9[a]
S_8 (N = 5)	2.1 ± 0.3	0.80 ± 0.02[b]	2.16 ± 0.06[a]	38 ± 1[a]	19.3 ± 2.5

Data are X ± SE.
[a] $P < 0.05$ vs. C, [b] vs. S_4

Table 3. Glomerular hemodynamics in the control, S_4 and S_7 groups

Group	SNGFR	Qa	SNFF	P_{GC}	P_T	ΔP	R_A	R_E	R_T	K_f
	nl/min			*mm Hg*			*×10*^{10} *· dyn · s · cm*^{5}			*nl/sec · mm Hg*
Control (N = 7)	26.17 ±2.22	63.41 ±6.05	0.42 ±0.02	41 ±1	14 ±1	27 ±2	4.19 ±0.39	1.58 ±0.14	5.58 ±0.50	0.059 ±0.004
S_4 (N = 8)	16.20[a] ±1.77	37.97[a] ±4.41	0.43 ±0.03	34[a] ±2	13 ±1	21[a] ±1	6.82[a] ±1.08	2.19 ±0.42	9.02[a] ±1.49	0.086 ±0.018
S_7 (N = 6)	23.08[b] ±0.96	54.35[b] ±2.36	0.43 ±0.03	40[b] ±1	14 ±1	27[b] ±2	3.32[b] ±1.06	1.73 ±0.21	5.05[b] ±0.62	0.058 ±0.009

Data are X ± SE. [a] $P < 0.05$ vs. group C, [b] vs. group S_4

plasma flow rate (Q_A) were also reduced in group S_4 ($P < 0.005$), but not in group S_7 ($P > 0.20$), when compared with control. In group S_7, SNGFR and Q_A were numerically lower than in the control group, but the difference was not statistically significant ($P > 0.10$). SNFF did not differ among the three groups.

Mean hydraulic pressures in proximal tubules (P_T), efferent arterioles (P_{EA}) and peritubular capillaries (P_C) were essentially the same for all groups, whereas mean glomerular capillary hydraulic pressure (P_{GC}) was significantly reduced in S_4 compared with control (34 ± 2 vs. 41 ± 1 mm Hg, $P < 0.005$), resulting in a reduced transglomerular hydraulic pressure difference (ΔP), that is, 21 ± 1 mm Hg in S_4 versus 27 ± 2 mm Hg in control ($P < 0.05$). P_{GC} and ΔP were normalized in S_7 group.

Table 4. Effects of captopril (Cp), indomethacin (Indo) and dazmegrel (Daz) on whole kidney function during 4 (S_4) or 7 (S_7) days of starvation

	MAP	V'	GFR	RPF	FF	TRVR
	mm Hg	*μl/min*	*ml/min*			*mm Hg · min · ml^{-1}*
Control (N = 14)	100 ± 3	2.1 ± 0.2	0.92 ± 0.06	3.69 ± 0.26	0.26 ± 0.01	14.7 ± 1.2
S_4 (N = 6)	96 ± 5	1.8 ± 0.2	0.57 ± 0.05[a]	2.15 ± 0.26[a]	0.28 ± 0.02	20.2 ± 2.4[a]
S_4 + Cp (N = 8)	88 ± 5[a]	2.0 ± 0.1	0.81 ± 0.04[b]	2.87 ± 0.16[a,b]	0.29 ± 0.01	14.4 ± 1.5[b]
S_4 + Indo (N = 7)	109 ± 5	2.2 ± 0.3	0.89 ± 0.04[b]	2.87 ± 0.27[a,b]	0.32 ± 0.01	17.7 ± 1.7
S_4 + Daz (N = 6)	102 ± 4	1.3 ± 0.1	0.65 ± 0.05[a]	1.81 ± 0.09[a]	0.36 ± 0.03	24.1 ± 0.8[a]
S_7 (N = 5)	92 ± 4	2.5 ± 0.5	0.84 ± 0.07[b]	2.13 ± 0.11[a]	0.41 ± 0.04[a]	19.3 ± 0.9[a]
S_7 + Cp (N = 7)	87 ± 3[a]	1.7 ± 0.1	0.58 ± 0.06[a,c]	2.41 ± 0.29[a]	0.25 ± 0.02	16.8 ± 2.8
S_7 + Indo (N = 7)	106 ± 5	1.6 ± 0.1	0.76 ± 0.04[b]	2.12 ± 0.09[a]	0.37 ± 0.02	20.9 ± 1.2[a]
S_7 + Daz (N = 6)	114 ± 3[c]	1.5 ± 0.1	0.63 ± 0.05[c]	1.60 ± 0.12[a]	0.39 ± 0.02	31.8 ± 3.2[a,c]

Data are X ± SE.
[a] $P < 0.05$ vs. group C, [b] vs. group S_4 and [c] vs. group S_7

Group S_4 showed an increase in R_T (Table 3) mainly due to a rise in R_A (63%), although a tendency toward elevation in R_E (38%) was also observed. Arteriolar resistances in group S_7 did not differ from the control group.

Since normal hydropenic rats were employed, only minimum values for K_f could be calculated and the mean values obtained were similar among groups (Table 3). Mean K_f obtained for group C was similar to values reported in the literature under hydropenic conditions [14].

The effects of renin-angiotensin, prostaglandin and thromboxane inhibition on groups S_4 and S_7 are summarized in Table 4.

Mean arterial pressure was reduced in groups receiving captopril ($P < 0.05$) compared with the control group, however, the values remained within the renal autoregulatory range (PAM > 80 mm Hg).

The effects of starvation for four days on whole kidney function were substantially blunted by captopril and indomethacin treatment but not by dazmegrel treatment. In groups S_4 + Cp and S_4 + Indo, mean GFR values were maintained near the control group values, that is, 0.81 ± 0.04 ml/min for S_4 + Cp and 0.89 ± 0.04 ml/min for S_4 + Indo versus 0.92 ± 0.06 ml/min for C ($P > 0.10$). Moreover, a partial improvement in RPF was obtained for both groups which maintained intermediate levels between the control and S_4 groups. TRVR was normalized in group S_4 + Cp ($P > 0.60$) but not in group S_4 + Indo ($P < 0.05$) when compared to control.

Captopril and dazmegrel treatment during seven days of starvation did not lead to GFR recovery (0.58 ± 0.06 ml/min in S_7 + Cp and 0.63 ± 0.05 ml/min in S_7 + Daz vs. 0.84 ± 0.07 ml/min in S_7; $P < 0.01$). In contrast, indomethacin administration (S_7 + Indo) did not produce significant changes in GFR or RPF values when compared with group S_7. A decrease in FF and an increase in TRVR were observed in this group.

Discussion

The main purpose of the present study was to evaluate the effects of progressive and prolonged starvation on renal function in rats. This model of food deprivation showed the occurrence of two phases of whole kidney function: an early phase (4 days), characterized by an abrupt decrease in RPF and an increase in TRVR followed by a gradual decline in GFR, and a late phase (7 days) in which a spontaneous normalization of GFR was observed despite reduced RPF and increased TRVR. Because of these non-proportional alterations in GFR and RPF, the FF changed during the eight days of starvation, thus during early phase, GFR declined more slowly than RPF, inducing an elevation in FF. When the decrease in GFR was proportional to that in RPF, FF tended to be not different from control (Groups S_3 to S_6). In the late phase, when GFR normalized and RPF was maintained but reduced, FF was again elevated.

The reductions in GFR and RPF observed in the early phase of starvation are frequently found during chronic malnutrition [15] and also in several models of food restriction [16, 17]. The decrease in GFR and SNGFR observed in this phase (S_4) was attributed to reduction in renal and glomerular plasma flow rates (RPF, Q_A), caused by elevations in renal vascular and arteriolar resistances. The contraction of extracellular volume might be involved in RPF reduction. However, acute volume replacement in rats starved for four days was not sufficient to correct GFR and RPF (data not shown).

In the S_4 group, the micropuncture data showed similarities between whole kidney and glomerular functions. After four days of food restriction, SNGFR and Q_A were reduced by 40%. Since mean P_T remained unchanged in S_4, the transglomerular hydraulic pressure difference (ΔP) decreased exclusively because of reduction in P_{GC}. R_T increased mainly due to an increment in R_A (63%), although a rise in R_E (39%) was also observed. The preferential afferent vasoconstriction was responsible for the reduction in Q_A and P_{GC}.

The glomerular ultrafiltration coefficient, K_f, remained unaltered in the S_4 group. The reason why K_f did not change is unclear. The existence of filtration pressure equilibrium observed during normal hydropenia prevents the determination of a single value for K_f, as discussed in detail by others [18], and minimum K_f values may not be sensitive enough to show differences between the groups. Moreover, when filtration pressure equilibrium is achieved ($\Delta P = \Pi_E$), SNGFR is insensitive to modifications in K_f [18], hence SNGFR is determined by C_A, ΔP and Q_A. Since C_A remained unchanged in the S_4 group throughout the experimental periods, the reduction in SNGFR is mainly attributed to decreases in ΔP and Q_A.

An elevation of GFR and SNGFR was observed after seven days of starvation. However, the normalization of GFR occurred despite altered RPF and TRVR, while Q_A and R_T normalized.

The micropuncture data from the S_7 group indicate that the normalization of SNGFR involves an adaptation of glomerular hemodynamics. The adaptative mechanism may start with readjustments of the arteriolar resistances, since R_A and R_E returned to control levels after seven days of food restriction. The proportional decrease in R_A and R_E provoked increases in P_{GC} and Q_A when compared with the S_4 group, both being responsible for elevation of SNGFR.

As discussed, the alterations in RPF and Q_A after four days of starvation were mainly caused by increases in renal arteriolar resistances, suggesting an intrarenal action of Ang II, since similar effects were obtained when exogenous Ang II was infused [19] or when high endogenous Ang II levels were induced [20].

Actually captopril as well as indomethacin prevented the decline in GFR induced after four days of starvation, and partially abolished the alterations in RPF and TRVR, suggesting that changes in renal function induced by starvation are hormone-mediated.

Captopril administration induced a reduction in MAP in S_4 and S_7, suggesting that Ang II is involved in the maintenance of systemic arterial pressure in the present situation. Moreover, the intrarenal vasodilatation induced by captopril in S_4 elevated RPF and consequently normalized GFR. Similar results were observed in low protein diet in rats, which also induces a reduction in GFR and RPF with elevation in TRVR [21–25]. It has been suggested that the low protein diet induces a prostaglandin-mediated impairment in the liberation of renin to the circulation, elevating the renal content of renin and thus increasing the intrarenal production of Ang II [24]. Captopril reversed this effect during low protein diet on GFR and RPF. However, it did not completely normalize the PGE_2 excretion, suggesting that the prostaglandins could have a permissive role in the renal hemodynamic alterations induced by low protein diet [25].

The relative vasodilatation of the renal vasculature induced by indomethacin after four days of food restriction suggests participation of a vasoconstrictor-PG component in this experimental situation. However, when the vasoconstrictor PG (TxA_2) was specifically blocked with dazmegrel, no protection of whole kidney function was observed. An alternative mechanism to explain the protective effect of indomethacin after four days of starvation may involve a relationship between the renin-angiotensin system (RAS) and PGs. It has been shown that prostaglandins of the E and I series can induce a rise in R_T and a decrease in Q_A and SNGFR when infused at nonvasodepressor doses [21]. Schor and Brenner [21] showed that these glomerular hemodynamics changes, usually observed after exogenous Ang II infusion were completely abolished by saralasin (Ang II antagonist), suggesting that the vasoconstrictor effect of PGE_2 and PGI_2 involves an intermediate action of Ang II. The present study showed that the PG system participates in the decline of GFR after four days of food restriction by a vasoconstrictor effect ($\downarrow$ TRVR by indomethacin).

It is interesting to note that Ang II presented opposite effects in S_4 and S_7, that is, Ang II blockade resulted in a protection of GFR in S_4, while in S_7 it did not correct GFR. Moreover, in contrast to what was observed in S_4, TxA_2 played a role in the maintenance of GFR in S_7, but not in S_4. Thus the results obtained in the late phase indicate that the presence of vasoconstrictor agents appear to be necessary for normalization of GFR. An alternative explanation may be an increase in kinins or PGs induced by captopril [23], leading to an imbalance in arteriolar resistance and impairing glomerular homeostasis.

Moreover, the normalization of GFR and SNGFR appears not to be dependent on prostaglandins, since indomethacin, despite the induction of an additional increment in TRVR, allowed GFR to return to control levels. Thus, captopril may have acted via the kinin system, impairing the normalization of GFR in S_7.

The whole kidney function assessment performed in groups with hormonal inhibition is indicative that angiotensin II and prostaglandins are hormones involved in the reduction of renal function, while after seven days of starvation Ang II and TxA_2 are involved in the normalization of GFR. However, the mechanisms by these hormones are influencing glomerular hemodynamics in these situations (days 4 and 7) need further investigation.

In summary, this model of acute malnutrition showed that the rat has an impressive adaptative ability to prolonged periods of starvation, with biphasic alterations of renal function involving an initial phase (4 days) characterized by the appearance of acute physiological renal failure, with similar responses of whole kidney and superficial glomerular functions. The fall in GFR was due to a decrease in RPF and an increase in TRVR. A disproportionate rise in arteriolar resistance ($R_A > R_E$) led to a decline in Q_A and P_{GC}, both responsible for the decrease in SNGFR. Moreover, the data strongly suggest a role of Ang II and PGs in the observed resistance elevation. In the late phase (7 days), GFR and SNGFR were normalized. However, differences between whole kidney and superficial glomerular functions were observed. Although SNGFR parameters (Q_A, P_{GC}, R_A, R_E and thus, R_T) were near control values after seven days of food restriction, RPF and TRVR did not recover, suggesting higher juxtamedullary nephron sensitivity. In this phase, the normalization of GFR and SNGFR depends, at least in part, on Ang II but not on PGs.

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